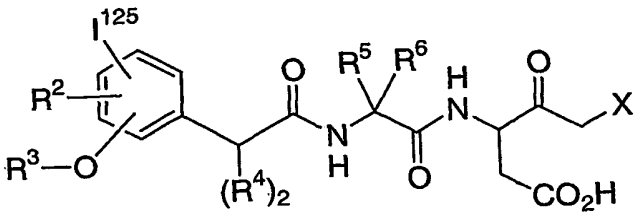
WHAT IS CLAIMED IS:

1. A compound represented by Formula I:



I

or a salt, ester or hydrate thereof, wherein:

X is halo, or

X is –O-W-Z, wherein W is a bond, -CH_2-, –C(O)- or –C(O)CH_2-;

Z is selected from the group consisting of:

(1) H,
(2) C_{1-11}alkyl,
(3) C_{3-11}cycloalkyl or a benzofused analog thereof,
(4) phenyl or naphthyl, and
(5) HET^1, wherein HET^1 represents a 5- to 10-membered mono- or bicyclic, aromatic or non-aromatic ring, or a benzofused analog thereof, containing 1-3 heteroatoms selected from O, S and N,

groups (2), (3) and (5) above are optionally substituted with 1-2 oxo groups,

groups (2) – (5) above are further optionally substituted with 1-3 substituents independently selected from the group consisting of:

(a) halo
(b) nitro,
(c) hydroxy,
(d) C_{1-4}alkyl,

(e) C_{1-4}alkoxy,
(f) C_{1-4}alkylthio,
(g) C_{3-6}cycloalkyl,
(h) phenyl or naphthyl,
(i) phenoxy,
(j) benzyl,
(k) benzyloxy, and
(l) a 5 or 6-membered aromatic or non-aromatic ring containing from 1-3 heteroatoms selected from O, S and N,

groups (d)-(g) above are optionally substituted with oxo and 1-3 substituents independently selected from halo and C_{1-4}alkoxy,

groups (h) – (l) above are optionally substituted with 1-3 substituents independently selected from halo and C_{1-4}alkyl, and

group (4) is further optionally substituted up to its maximum with halo groups;

R^2 is selected from the group consisting of:
(1) H,
(2) halo,
(3) hydroxy,
(4) nitro,
(5) cyano,
(6) C_{1-10}alkyl, C_{3-10}cycloalkyl, C_{1-10}alkoxy, $-S(O)_{0-2}C_{1-10}$alkyl or $-NHC_{1-10}$alkyl, each optionally substituted with 1-2 oxo or carboxy groups and further optionally substituted with 1-3 substituents independently selected from the group consisting of:
(a) halo,
(b) hydroxy
(c) cyano,
(d) C_{1-4}alkoxy,
(e) $-NHR^7$, wherein R^7 is independently H or C_{1-5}alkyl,
(f) $-S(O)_{0-2}C_{1-4}$alkyl, and

(g) HET^2, wherein HET^2 represents a 5- to 7-membered aromatic or non-aromatic ring containing 1-4 heteroatoms selected from O, S and NR^8, wherein R^8 is independently H or C_{1-5}alkyl, said HET^2 being optionally substituted with oxo and further optionally substituted with 1-2 substituents independently selected from halo and C_{1-4}alkyl, said C_{1-4}alkyl being optionally substituted with 1-3 halo groups,

(7) phenoxy or -S(O)$_{0-2}$phenyl,

(8) benzyloxy or -S(O)$_{0-2}$benzyl,

(9) benzoyl,

(10) phenyl or naphthyl,

(11) -O-HET^2 or –S-HET^2, said HET^2 being optionally substituted with oxo and further optionally substituted as defined below, and

(12) HET^3, wherein HET^3 is a 5- or 6-membered aromatic or non-aromatic ring, or a benzofused analog thereof, containing from 1 to 4 heteroatoms selected from O, S and N, said HET^3 being optionally substituted with oxo and further optionally substituted as defined below,

groups (7) - (12) above are each optionally substituted with 1-2 substituents independently selected from the group consisting of: halo, cyano, C_{1-4}alkyl and C_{1-4}alkoxy, said C_{1-4}alkyl and C_{1-4}alkoxy being optionally substituted with 1-3 halo groups;

R^3 is phenyl or C_{1-10}alkyl, said C_{1-10}alkyl optionally substituted with 1-2 oxo or carboxy groups and further optionally substituted with 1-3 substituents independently selected from the group consisting of:

(a) halo,

(b) hydroxy

(c) cyano,

(d) C_{1-4}alkoxy,

(e) -NHR^7, wherein R^7 is independently H or C_{1-5}alkyl,

(f) -S(O)$_{0-2}C_{1-4}$alkyl, and

(g) HET^2, wherein HET^2 represents a 5- to 7-membered aromatic or non-aromatic ring containing 1-4 heteroatoms selected from O, S and NR^8, wherein R^8 is independently H or C_{1-5}alkyl, said HET^2 being optionally substituted with oxo and further optionally substituted with 1-2 substituents independently selected from halo or C_{1-4}alkyl, said C_{1-4}alkyl being optionally substituted with 1-3 halo groups,

each R^4 is independently selected from the group consisting of: H, halo, hydroxy, C_{1-6}alkyl and C_{1-4}alkoxy, said C_{1-6}alkyl and C_{1-4}alkoxy being optionally substituted with oxo and further optionally substituted with 1-3 halo groups; and

R^5 is selected from the group consisting of: H, phenyl, naphthyl, C_{1-6}alkyl optionally substituted with OR^{12} and 1-3 halo groups, and C_{5-7} cycloalkyl optionally containing one heteroatom selected from O, S and NR^{13},

wherein R^{12} is selected from the group consisting of: H, C_{1-5}alkyl optionally substituted with 1-3 halo groups, and benzyl optionally substituted with 1-3 substituents independently selected from halo, C_{1-4}alkyl and C_{1-4}alkoxy, and

R^{13} is H or C_{1-4}alkyl optionally substituted with 1-3 halo groups; and

R^6 represents H;

or in the alternative, R^5 and R^6 are taken in combination and represent a ring of 4-7 members, said ring optionally containing one heteroatom selected from O, S and NR^{13}.

2. The compound according to Claim 1 wherein X is halo.

3. The compound according to Claim 1 wherein X is –O-W-Z.

4. The compound according to Claim 3 wherein Z is selected from the group consisting of:

(1) C_{1-11}alkyl,
(2) C_{3-11}cycloalkyl or a benzofused analog thereof, and
(3) phenyl or naphthyl,

wherein groups (1) – (3) above are optionally substituted with 1-3 substituents independently selected from the group consisting of:

(a) halo
(b) nitro,

(c) hydroxy,
(d) C_{1-4}alkyl,
(e) C_{1-4}alkoxy,
(f) C_{1-4}alkylthio,
(g) C_{3-6}cycloalkyl,
(h) phenyl or naphthyl,
(i) phenoxy,
(j) benzyl and
(k) benzyloxy.

5. The compound according to Claim 1 wherein R^3 is methyl.

6. The compound according to Claim 1 wherein R^2 and each R^4 are hydrogen.

7. The compound according to Claim 1 wherein R^5 is selected from the group consisting of: C1-6alkyl, phenyl and naphthyl.

8. The compound according to Claim 1 wherein:

X is halo or –O-W-Z;

W is a bond, -CH_2-, –C(O)- or –C(O)CH_2-;

Z is selected from the group consisting of:
(1) C_{1-6}alkyl, optionally substituted with 1-3 halo groups,
(2) C_{3-11}cycloalkyl or a benzofused analog thereof, and
(3) phenyl or naphthyl, optionally substituted with 1-3 groups independently selected from halo or C_{1-4}alkyl,

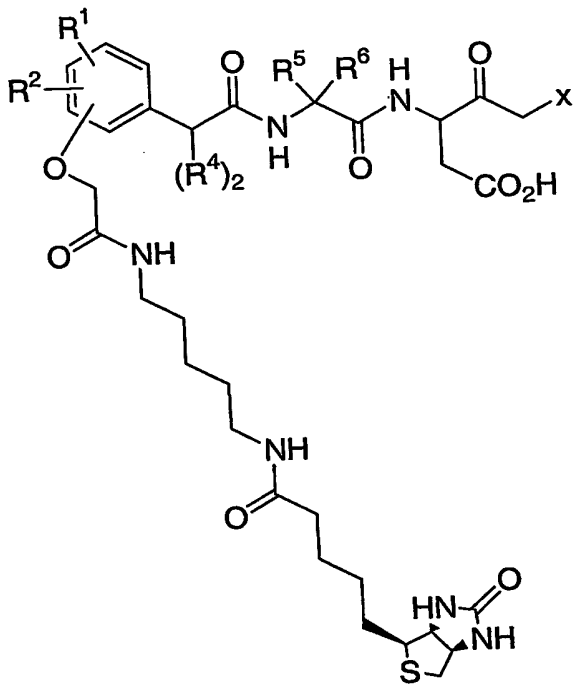
R^3 is methyl, ethyl or phenyl;

R^2 and each R^4 are hydrogen;

R5 is selected from the group consisting of: C1-6alkyl, C5-7cycloialkyl, phenyl and naphthyl; and

R6 is hydrogen.

9. A compound of Formula II



II

or a salt, ester or hydrate thereof, wherein:

X is halo;

R1 and R2 are each independently selected from the group consisting of:

(1) H,
(2) halo,
(3) hydroxy,

(4) nitro,

(5) cyano,

(6) C_{1-10}alkyl, C_{3-10}cycloalkyl, C_{1-10}alkoxy, $-S(O)_{0-2}C_{1-10}$alkyl or $-NHC_{1-10}$alkyl, each optionally substituted with 1-2 oxo or carboxy groups and further optionally substituted with 1-3 substituents independently selected from the group consisting of:

(a) halo,

(b) hydroxy

(c) cyano,

(d) C_{1-4}alkoxy,

(e) $-NHR^7$, wherein R^7 is independently H or C_{1-5}alkyl,

(f) $-S(O)_{0-2}C_{1-4}$alkyl, and

(g) HET^2, wherein HET^2 represents a 5- to 7-membered aromatic or non-aromatic ring containing 1-4 heteroatoms selected from O, S and NR^8, wherein R^8 is independently H or C_{1-5}alkyl, said HET^2 being optionally substituted with oxo and further optionally substituted with 1-2 substituents independently selected from halo and C_{1-4}alkyl, said C_{1-4}alkyl being optionally substituted with 1-3 halo groups,

(7) phenoxy or $-S(O)_{0-2}$phenyl,

(8) benzyloxy or $-S(O)_{0-2}$benzyl,

(9) benzoyl,

(10) phenyl or naphthyl,

(11) $-O-HET^2$ or $-S-HET^2$, said HET^2 being optionally substituted with oxo and further optionally substituted as defined below, and

(12) HET^3, wherein HET^3 is a 5- or 6-membered aromatic or non-aromatic ring, or a benzofused analog thereof, containing from 1 to 4 heteroatoms selected from O, S and N, said HET^3 being optionally substituted with oxo and further optionally substituted as defined below,

groups (7) - (12) above are each optionally substituted with 1-2 substituents independently selected from the group consisting of: halo, cyano, C_{1-4}alkyl and C_{1-4}alkoxy, said C_{1-4}alkyl and C_{1-4}alkoxy being optionally substituted with 1-3 halo groups;

R^3 is C_{1-10}alkyl, optionally substituted with 1-2 oxo or carboxy groups and further optionally substituted with 1-3 substituents independently selected from the group consisting of:

(a) halo,

(b) hydroxy
(c) cyano,
(d) C_{1-4}alkoxy,
(e) -NHR^7, wherein R^7 is independently H or C_{1-5}alkyl,
(f) -$S(O)_{0-2}C_{1-4}$alkyl, and
(g) HET^2, wherein HET^2 represents a 5- to 7-membered aromatic or non-aromatic ring containing 1-4 heteroatoms selected from O, S and NR^8, wherein R^8 is independently H or C_{1-5}alkyl, said HET^2 being optionally substituted with oxo and further optionally substituted with 1-2 substituents independently selected from halo or C_{1-4}alkyl, said C_{1-4}alkyl being optionally substituted with 1-3 halo groups,

each R^4 is independently selected from the group consisting of: H, halo, hydroxy, C_{1-6}alkyl and C_{1-4}alkoxy, said C_{1-6}alkyl and C_{1-4}alkoxy being optionally substituted with oxo and further optionally substituted with 1-3 halo groups; and

R^5 is selected from the group consisting of: H, phenyl, naphthyl, C_{1-6}alkyl optionally substituted with OR^{12} and 1-3 halo groups, and C_{5-7} cycloalkyl optionally containing one heteroatom selected from O, S and NR^{13},

wherein R^{12} is selected from the group consisting of: H, C_{1-5}alkyl optionally substituted with 1-3 halo groups, and benzyl optionally substituted with 1-3 substituents independently selected from halo, C_{1-4}alkyl and C_{1-4}alkoxy, and

R^{13} is H or C_{1-4}alkyl optionally substituted with 1-3 halo groups; and

R^6 represents H;

or in the alternative, R^5 and R^6 are taken in combination and represent a ring of 4-7 members, said ring optionally containing one heteroatom selected from O, S and NR^{13}.

10. The compound according to Claim 9 wherein:

R^1 is selected from the group consisting of:
(1) halo,

(2) C_{1-4}alkyl or C_{1-4}alkoxy, each optionally substituted with oxo and 1-3 halo groups, and

(3) HET^3, wherein HET^3 is a 5- or 6-membered aromatic or non-aromatic ring, or a benzofused analog thereof, containing from 1 to 4 heteroatoms selected from O, S and N, and optionally substituted with 1-2 substituents independently selected from halo and C_{1-4}alkyl, said C_{1-4}alkyl being optionally substituted with 1-3 halo groups;

R^2 and each R^4 are hydrogen;

R^5 is selected from the group consisting of: C1-6alkyl, phenyl and naphthyl; and

R6 is hydrogen.

11. The compound according to Claim 10 wherein HET^3 is 1,2,4-oxadiazole, optionally substituted with C_{1-4}alkyl.

12. A method for detecting active caspase-3 in cells or tissues of a mammal comprising contacting said cells or tissues with a compound of Claim 1 and detecting active caspase-3.

13. A method for detecting active caspase-3 in cells or tissues of a mammal comprising contacting said cells or tissues with a compound of Claim 9 and detecting active caspase-3.

14. A method for determining the caspase-3 active site occupancy of a sample reversible caspase-3 inhibitor in an animal model of cellular injury comprising:

1) administering to said animal said sample reversible caspase-3 inhibitor;
2) euthanizing said animal and extracting said injured cells;
3) contacting said injured cells *ex vivo* with a compound according to Claim 1;
4) detecting the amount of said compound to determine the number of caspase-3 free active sites; and

5) comparing said number of caspase-3 free active sites to the total measure of active caspases to determine the caspase-3 active site occupancy.

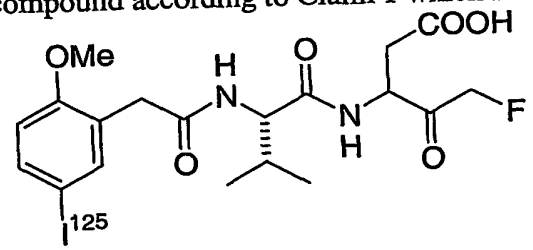
15. A method for determining the caspase-3 active site occupancy of a sample reversible caspase-3 inhibitor in a cell culture comprising:

1) contacting said cell culture with a sample reversible caspase-3 inhibitor;
2) contacting said cell culture with a compound according to Claim 1;
3) detecting the amount of said compound to determine the number of caspase-3 free active sites; and
4) comparing said number of caspase-3 free active sites to the total measure of active caspases to determine the caspase-3 active site occupancy.

16. A kit for detecting active caspase-3 in cells or tissues of a mammal comprising a compound of Claim 1.

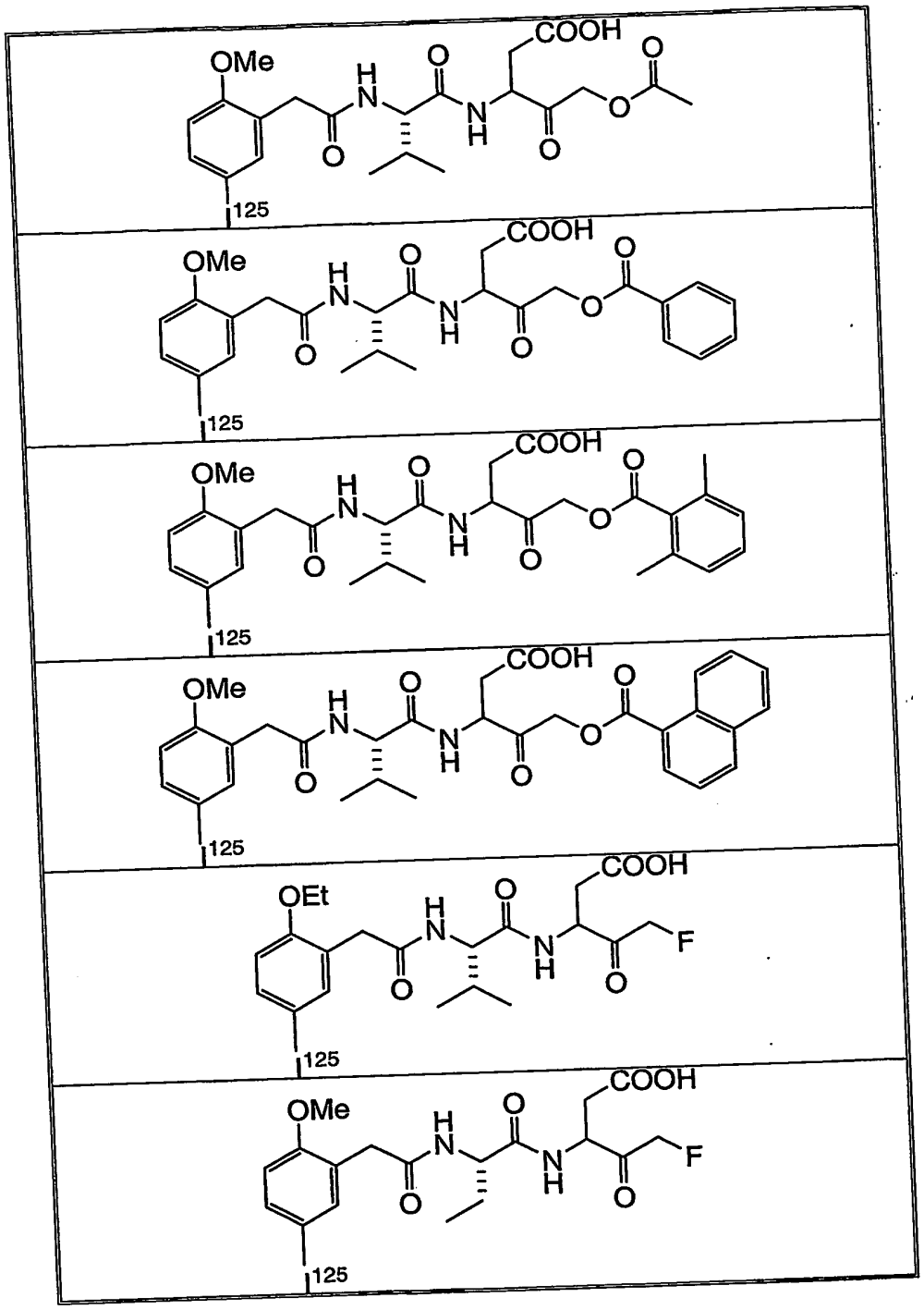
17. A kit for detecting active caspase-3 in cells or tissues of a mammal comprising a compound of Claim 9.

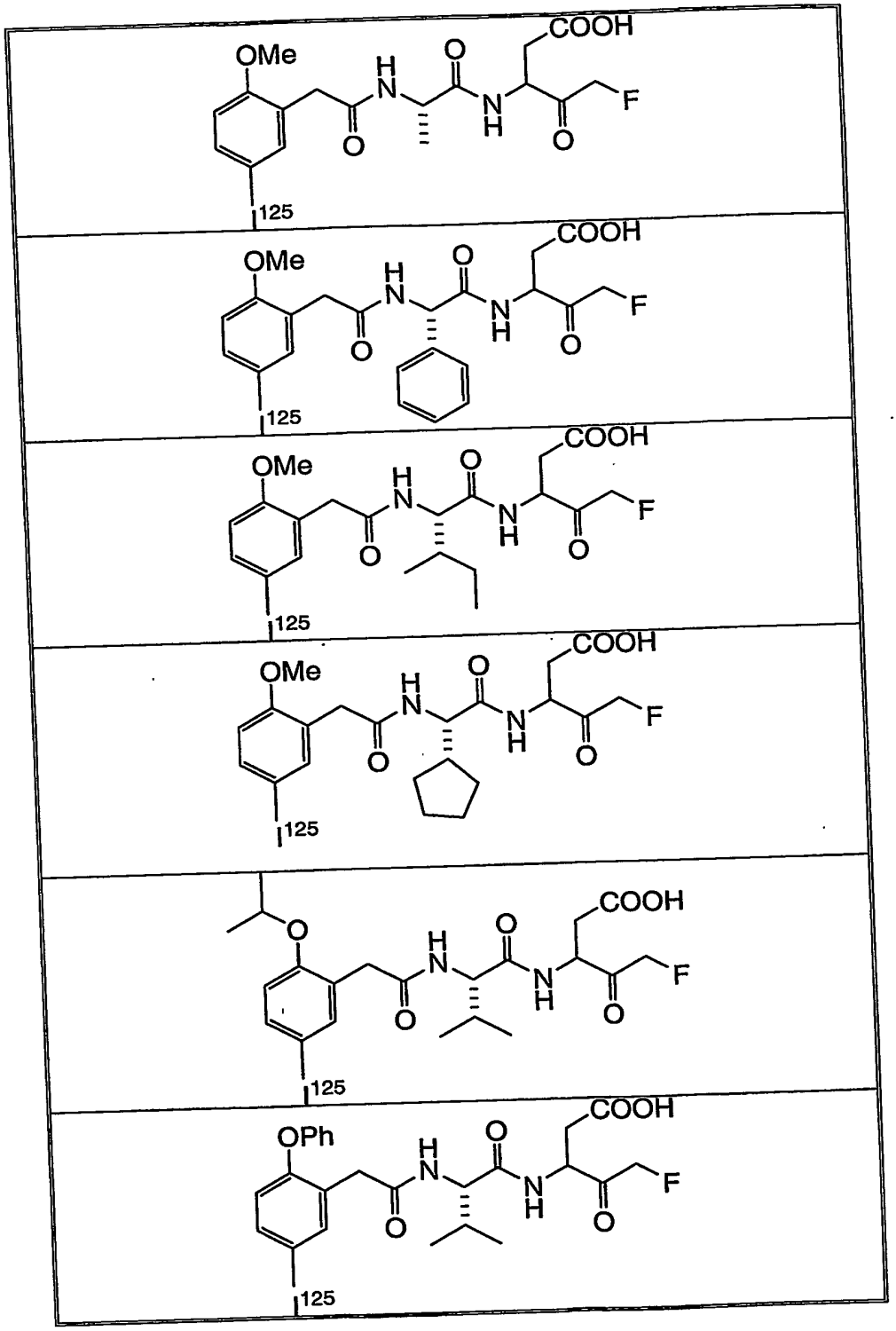
18. The compound according to Claim 1 which is

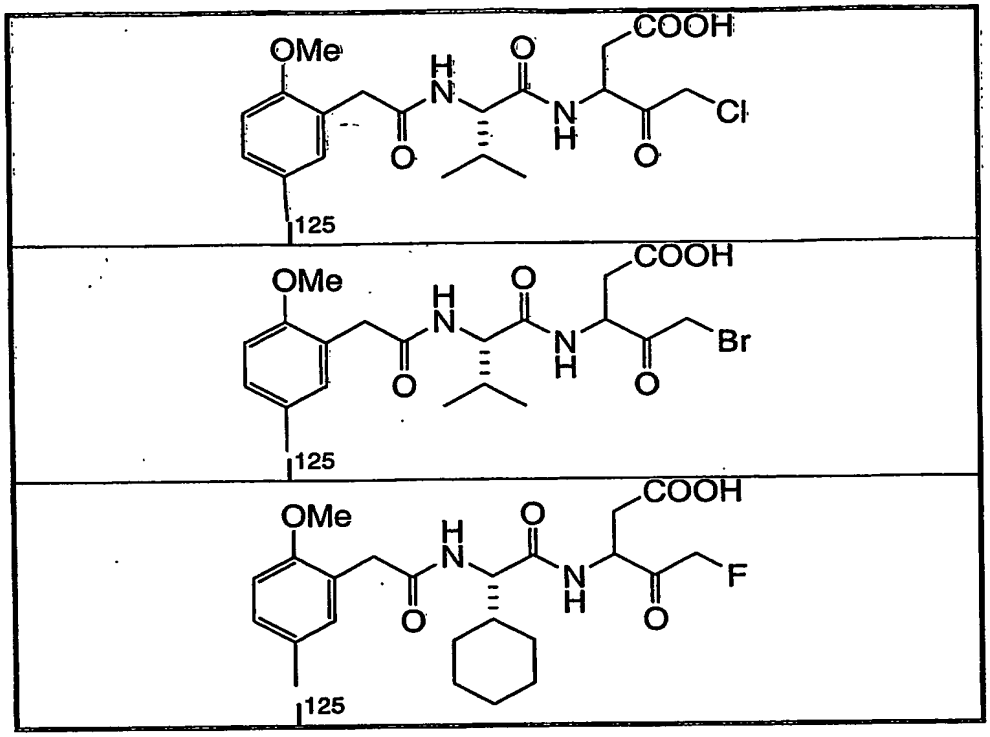


or a salt, ester or hydrate thereof.

19. A compound according to Claim 1 which is selected from the following table:


OMe
COOH
125
OMe
COOH
125
OMe
COOH
125
OMe
COOH
125
OEt
COOH
F
125
OMe
COOH
F
125


OMe
COOH
F
125
OMe
COOH
F
125
OMe
COOH
F
125
OMe
COOH
F
125
COOH
F
125
OPh
COOH
F
125



or a salt, ester or hydrate of any of the above.

20. A compound of any one of claims 1 to 11, 18 or 19 for use in detecting active caspase-3 in cells or tissues of a mammal.

21. A compound of any one of clams 1 to 11, 18 or 19 for use in determining the caspase-3 active site occupancy of a sample reversible capase-3 inhibitor in an animal model of cellular injury.